Remarks

The Amendments

Claim 43 has been amended to recite "producing a population of first strand cDNA" in place of "producing a population of cDNA." The amendment merely provides antecedent basis for "said population of first strand cDNA," which is later recited in claim 43.

Claim 69 has been amended to properly recite dependency on claim 68 in place of claim 43.

Claim 73 has been amended to additionally recite that "the first strand cDNA is synthesized using a polymerase that has reverse transcriptase activity." The amendment is supported by the specification which discloses, "A population of mRNA derived from cells in a sample is reverse transcribed to form a population of first strand cDNA hybridized to said mRNA." (Page 2, lines 17-19.) The amendment is also supported by claim 71.

The specification has been amended at the Brief Description of the Drawings to refer to "Figure 1" in place of "The figure."

These amendments introduce no new matter.

Specification

The specification has been objected to because the Brief Description of the Drawings does not refer to a Figure by number. The specification has been amended to refer to the Figure as "Figure 1." Applicants respectfully request withdrawal of the objection.

The Rejection of Claim 73 Under 35 U.S.C. § 112, Second Paragraph

Claim 73 has been rejected under 35 U.S.C. § 112, second paragraph as indefinite. Applicants respectfully traverse.

The Office Action asserts that claim 73 is unclear because the recitation "said reverse transcriptase" lacks antecedent basis. Claim 73 has been amended to include the recitation that a "first stand cDNA is synthesized using a polymerase that has reverse transcriptase activity." The recitation provides antecedent basis for "said reverse transcriptase."

Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 43-46, 49-52, 56, 58, 60-70, 74, and 76 Under 35 U.S.C. § 103(a)

Claims 43-46, 49-52, 56, 58, 60-70, 74, and 76 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Mack (U.S. Patent 6,303,301) in view of Wei (U.S. Patent 5,851,802). Applicants respectfully traverse.

The Patent Office has the burden of establishing a *prima facie* case of obviousness. (MPEP § 2142.) To establish *prima facie* obviousness of a claimed invention there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992). The teachings of the references are considered in their entirety including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983).

Claim 43 is the only independent claim of the rejected claim set. Claim 43 is directed to a method for analyzing a population of RNA. The method comprises a step of producing a

population of first strand cDNA from a population of mRNA. The population of first strand cDNA is produced using a primer having a first and a second portion. The first portion is complementary to a plurality of RNA molecules in the population and the second portion comprises a promoter sequence. The first portion is 3' to the second portion. Second strand cDNA that is complementary to the population of first strand cDNA is synthesized by extending random oligomers to form a population of double stranded cDNA. A population of cRNA is created from the double stranded cDNA. The population of cRNA is hybridized to an array. A resulting hybridization pattern is analyzed.

The Office Action cites Mack as teaching all steps of the claimed method except that of synthesizing second strand cDNA using random oligomers. (Paper 14, page 3, line 22 to page 4, line 11.) The Office Action cites Wei as teaching the use of random oligomers that anneal to first strand cDNA to produce second strand cDNA. (Paper 14, page 4, lines 12-13.) The Office Action states that one of ordinary skill in the art would have been motivated to modify Mack's step of synthesizing a second strand of cDNA with Wei's teaching that random oligomers can be used to prime second strand cDNA synthesis because "Wei et al. states that the random hexamer method provides a more efficient method for producing second strand cDNA. It would have been prima facie obvious to apply Wei et al.'s teaching of random primers to Mack's cDNA synthesis method in order to efficiently produce the second strand cDNA." (Paper 14, page 4, lines 16-19.)

Wei, however, provides no teaching that would motivate one of ordinary skill in the art to select random oligomers to synthesize the second strand of double stranded cDNA. Wei teaches four methods for synthesizing the second strand of cDNA:

> 1) An RNAse, such as RNAse H, can be used to generate nicks in the mRNA strand of the mRNA/cDNA hybrid, and then a DNA polymerase, such as the Klenow fragment of *E. coli* DNA polymerase I, can be used to produce the second strand of cDNA by *replacement synthesis*;
> 2) Hairpin structures usually form at the 3' end of first strand cDNA. These hairpins can be digested with an endonuclease, such as nuclease S1, and then used to prime the synthesis of the second strand of cDNA by DNA polymerases, such as the Klenow fragment;
> 3) Arbitrary DNA sequence can be added to the 3' end of the first strand cDNA, either by terminal transferases or RNA ligases, such as T4 RNA ligase, and oligodeoxynucleotides complementary to these arbitrary DNA sequences can be annealed to prime the synthesis of the second strand of cDNA by DNA polymerases, such as the Klenow fragment;
> 4) Oligodeoxynucleotides, such as random hexamers, can be annealed to the first strand cDNA and extended by a DNA polymerase, such as the Klenow fragment, to produce the second strand of cDNA.

Column 10, lines 34-53, emphasis added. Wei teaches that one of these four methods is preferred for synthesizing second strand cDNA because it is more efficient at second strand cDNA synthesis. That method, however, is not the random oligomer method as asserted in the Office Action. Wei teaches, "*Replacement synthesis* has been shown to be particularly efficient for producing the second strand of cDNA." (Column 10, lines 54-55, emphasis added.) Replacement synthesis (method 1) is not the random primer method (method 4). Wei thus would not have motivated one of ordinary skill in the art to modify Mack's method of analyzing cellular mRNA by employing random oligomer primers to synthesize second strand cDNA. At most, Wei would have motivated one of ordinary skill in the art to use replacement synthesis.

Moreover, Wei teaches *away* from using random oligomers to synthesize the second cDNA strand. Wei reviews a method taught by Liang and Pardee. The Liang and Pardee method generated a cDNA representation of essentially all mRNA expressed in a cell and

included a step of producing of double stranded cDNA from mRNA. Liang and Pardee produced the second strand of the double stranded cDNA using primers of an arbitrary, *i.e.*, random, sequence. Wei teaches that using the random primers has disadvantages. Wei teaches that short random primers anneal nonspecifically to first strand cDNA. Wei teaches that long random primers create a cDNA population that is not representative of all the mRNA expressed in a cell.

> The length of the second oligodeoxynucleotide of arbitrary sequence (random primer) to be used represents a necessary compromise. In order to recognize as many mRNA species as possible, Liang and Pardee (1992) calculated that the second primer of arbitrary sequence needed to be a 6-mer or 7-mer. However, in order to amplify a specific sequence with a high degree of specificity using the PCR procedure, the arbitrary sequence primer needed to be as long as possible.

Wei at column 3, lines 25-33. Thus, the teachings of Wei, considered in their entirety, would have directed one of ordinary skill in the art away from using random oligomers to synthesize second strand cDNA in Mack's method.

Mack also provides no teaching that would motivate one of ordinary skill in the art to select random oligomer primers to synthesize the second cDNA strand of double stranded cDNA. Mack teaches production of double stranded cDNA from mRNA. However, Mack does not suggest any particular type of primer or method that should be used to synthesize the second strand of the double stranded cDNA. Mack teaches that "Poly A^+ RNA [is] isolated and used as template for double stranded cDNA (ds cDNA) synthesis using an oligo dT primer containing a T7 promoter sequence at its 5' end." (Column 32, lines 20-22.) Mack is silent on second strand cDNA synthesis. Mack simply does not supply any motivation to use any particular type of primer, *e.g.*, a random oligomer, to prime synthesis of the second cDNA strand.

One of ordinary skill in the art would not have been motivated to modify Mack's method of analyzing cellular mRNA to include the use of Wei's random oligomer primers during second cDNA strand synthesis. Wei teaches that the most efficient method to synthesize the second cDNA strand is replacement synthesis, not synthesis using random oligomers, and that the use of random oligomers has disadvantages. There is no motivation to combine Mack and Wei to arrive at the claimed invention. Thus the case of *prima facie* obviousness must fail. Applicants respectfully request withdrawal of this rejection of claim 43.

If an independent claim is nonobvious under 35 U.S.C. 103, then any claim dependent therefrom is nonobvious. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988). Claims 44-46, 49-52, 56, 58, 60-70, 74, and 76 depend from claim 43. Therefore, they too should be found allowable. Applicants also respectfully request withdrawal of the rejection to these claims.

The Rejection of Claims 47, 48, 53-55, and 71-73 Under 35 U.S.C. § 103(a)

Claims 47, 48, 53-55, and 71-73 are rejected under 35 U.S.C. § 103(a) as unpatentable over Mack (U.S. Patent 6,303,301) in view of Wei (U.S. Patent 5,851,802) in further view of Van Gelder (U.S. Patent 5,891,636). Applicants respectfully traverse.

All of the claims in the rejected claim set depend from claim 43. As discussed above, Mack is cited as teaching all steps of the claimed method except that of synthesizing second strand cDNA using random oligomers (paper 14, page 3, line 22 to page 4, line 11), and Wei is cited as teaching synthesizing second strand cDNA using random hexamers (paper 14, page 4, lines 12-13). Van Gelder is further cited as teaching elements in dependent claims not taught by Mack or Wei, such as the use of myeloblastoma virus reverse transcriptase (claims 71-73), use of

E. coli DNA polymerase I to synthesize second strand cDNA (claims 53 and 55), and use of T3 promoter (claim 47), and SP6 promoter (claim 48). (Paper 14, page 5, lines 7-9.)

As discussed above, one of ordinary skill in the art would not have been motivated to modify the cellular mRNA analysis method taught by Mack to include the use of random oligomers to prime second strand cDNA synthesis as taught by Wei. Mack teaches production of double stranded cDNA from mRNA. However, Mack does not suggest any particular type of primer that should be used to synthesize the second strand of the double stranded cDNA. (Column 32, lines 20-22.)

Wei teaches using a random oligomer primer to synthesize the second cDNA strand of double-stranded cDNA. However, Wei teaches that the use of the random oligomer primer is one of four methods that can be used to synthesize the second cDNA strand. Wei teaches that of the four methods strand displacement, not random oligomer primers, is the most efficient method. (Column 10, lines 54-55.) Wei also teaches that use of random oligomers to synthesize a second cDNA strand has the disadvantage of either sacrificing specific annealing of the primer to the first cDNA strand or provides an incomplete representation of the mRNA expressed in a cell. (Column 3, lines 25-33.)

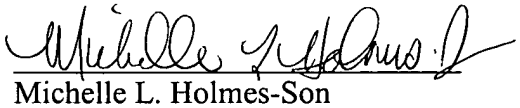
Van Gelder also fails to supply any teaching that would motivate one of ordinary skill in the art to modify the teachings of Mack with the teachings of Wei to synthesize the second strand of cDNA using random oligomers. Van Gelder teaches methods of producing double stranded cDNA from mRNA. Van Gelder, like Wei, teaches that the preferred method of synthesizing the second strand of the cDNA is replacement synthesis. Van Gelder teaches, "The second strand cDNA, creating double-stranded (ds) cDNA, can be synthesized by a variety of means, but preferably with the addition of RNase H and *E. coli* DNA polymerase." (Column 5, lines 8-11.)

Van Gelder does not teach the use of random oligomer primers to synthesize second cDNA strands. Thus Van Gelder fails to supply the missing motivation to modify Mack's method of analyzing cellular mRNA such that the step of synthesizing the second strand of double stranded cDNA is performed using random oligomers as taught by Wei.

Wei and Van Gelder would not have motivated one of ordinary skill in the art to have modified Mack's teachings to arrive at the claimed invention. Thus the *prima facie* case of obviousness against claim 43 must fail. Claims 47, 48, 53-55, and 71-73 depend from claim 43. If an independent claim is nonobvious under 35 U.S.C. 103, then any claim dependent therefrom is nonobvious. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988). Thus applicants respectfully request withdrawal of this rejection to claims 47, 48, 55-58, and 71-73.

Respectfully submitted,

Dated: July 9, 2003

By: 
Michelle L. Holmes-Son
Reg. No. 47,660

BANNER & WITCOFF
1001 G Street, N.W., Eleventh Floor
Washington, D.C. 20001-4597
(202) 824-3000